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| FOLEY & LARDNER LLP | | | ANDERSON, JAMES D | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--------------------------------------|--------------------------------------|
| Office Action Summary | Application No. 10/790,943 | Applicant(s) WILSON ET AL. |
| | Examiner JAMES D. ANDERSON | Art Unit 1614 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 20 August 2008.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-4,7,8,11-13,16,17,20 and 21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-4,7,8,11-13,16,17,20 and 21 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date 8/20/2008, 9/4/2008, 12/3/2008
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
 5) Notice of Informal Patent Application
 6) Other: _____

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 8/20/2008, are acknowledged and entered. Claims 1-4, 7, 8, 11-13, 16, 17, and 20-21 are pending and under examination.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 8/20/2008, 9/4/2008, and 12/3/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. DE 19721211A1 and DE 2015265A1 cited as references F1 and F2 on the IDS filed 8/20/2008 were not considered because they are not in English and no translation was provided. Reference D28 on the IDS filed 8/20/2008 was also not considered because no date of publication is provided. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-4, 7-8, 11-13, 16-17, and 20-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding the abbreviation DMXAA, is withdrawn in light of Applicant's amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-4, 7-8, 11-13, 16-17, and 20-21 under 35 U.S.C. 103(a) as being unpatentable over **Davis** (WO 00/48591; Published 8/24/2000) (cited by Applicants in IDS filed 10/31/2007) in view of Applicants' disclosure at page 9, line 14 and page 12, lines 17-19 is withdrawn in view of Applicant's arguments. Davis does not teach gemcitabine as recited in the instant claims and Applicant's disclosure of gemcitabine is found in the summary of the present invention, not in the background section.

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over **Siemann et al.** (Proceedings of the American Association for Cancer Research, 2000, vol. 41, page 525) and **Pruijn et al.** (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546) in view of **Grindley et al.** (USP No. 5,464,826; Issued Nov. 7, 1995) (newly cited) and **van Moorsel et al.** (Biochemical Pharmacology, 1999, vol. 57, pages 407-415).

The instant claims are drawn to methods, compositions, and kits comprising DMXAA and gemcitabine. Dependent claims recite that the agents are in a potentiating ratio.

Siemann et al. teach that DMXAA enhances (*i.e.* potentiates) the efficacy of the chemotherapeutic agents cisplatin and cyclophosphamide in rodent (KHT sarcoma) and human (SKBR3 breast and OW1 ovarian carcinoma) tumor models. DMXAA (17.5 mg/kg) was shown to increase the tumor cell kill of cisplatin and cyclophosphamide by 10-500-fold over that seen

with chemotherapy alone (Abstract). The reference thus demonstrates that DMXAA potentiates the antitumor effect of two traditional chemotherapeutic agents in a mammalian tumor model of breast and ovarian tumors.

Prujin *et al.* also teach enhancing the antitumor activity of an anticancer agent, in this case melphalan, by co-administering melphalan with DMXAA (Abstract). DMXAA is well known in the art as an antitumor agent that inhibits tumor blood flow (page 541, right column, "Introduction"). DMXAA is also disclosed to enhance the antitumor effects of hypoxia-selective cytotoxins (*id.*). DMXAA was formulated in phosphate-buffered saline and melphalan was dissolved in 60% propylene glycol with 40% sodium citrate and both solutions were injected *i.p.* (page 542, left column, "Materials and Methods"). The reference thus motivates one skilled in the art to formulate the compositions recited in instant claims 7-8, 11-13, 16-17, and 20-21. Figure 1 (page 543) demonstrates that DMXAA and melphalan can be administered concomitantly or sequentially and in both cases DMXAA potentiates the effect of melphalan. The reference thus expressly suggests concomitant and sequential administration as recited in claims 3-4. The reference thus expressly suggests that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the alkylating agent caused by falling tumor blood flow (page 545, right column, last full paragraph). One skilled in the art would have been imbued with at least a reasonable expectation that DMXAA would have this effect on any known anticancer agent, including the instantly claimed gemcitabine. The authors conclude that the study demonstrates the potential of DMXAA to "induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions (*id.*).

The primary and secondary references do not explicitly teach combining DMXAA with gemcitabine as recited in the instant claims.

Grindley *et al.* is provided as evidence that the instantly claimed gemcitabine was a compound known to be effective in treating cancer, including the instantly claimed solid tumors. In this regard, Grindley *et al.* teach a class of 2',2'-difluoronucleosides that can be used to treat neoplasms (Abstract). With respect to gemcitabine, this compound is exemplified at column 10, lines 7-8; Table 1; and claims 2, 4-5, and 7. With respect to solid tumors, Grindley *et al.* teach

that the compounds of the invention can be used to treat tumors, both solid and non-solid type (col. 16, lines 13-15). Compositions and formulations as recited in claims 7-8, 11-13, 16-17, and 20-21 are disclosed at column 16, lines 20-63. Grindley *et al.* do not teach combining gemcitabine with other anticancer agents.

However, van Moorsel *et al.* disclose combination chemotherapy studies with gemcitabine and etoposide in non-small cell lung and ovarian cancer cell lines. These antineoplastic agents are known in the art to have clinical activity against various solid tumors (Abstract). Because gemcitabine and etoposide have different mechanisms of action, the drugs were combined and studied *in vitro*. Gemcitabine has clinical activity in several solid tumors, such as ovarian cancer, NSCLC, head and neck cancer, and pancreatic cancer (page 407). Gemcitabine becomes phosphorylated to its triphosphate and is subsequently incorporated into DNA, followed by one or more deoxynucleotides after which DNA polymerization stops. Etoposide is a widely used anticancer agent that inhibits topoisomerase II (pages 407-408). Gemcitabine was solubilized in PBS for the experiments (page 408). The combined chemotherapy was shown to be synergistic in ovarian and NSCLC cells lines (Table 2). The reference thus motivates combining gemcitabine with other anticancer agents in the treatment of cancer and further demonstrates that such a combination could be synergistic in nature.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer DMXAA in combination with gemcitabine as taught by Siemann *et al.* and Pruijn *et al.* in view of Grindley *et al.* and van Moorsel *et al.* One would have been motivated to do so because each of the therapeutics instantly claimed (DMXAA and gemcitabine) have been individually taught in the prior art to be successful at treating cancer, and further, Siemann *et al.* and Pruijn *et al.* explicitly teach combination therapy for the treatment of cancer using DMXAA and a second therapeutic agent. Further still, van Moorsel *et al.* teach combination therapy comprising gemcitabine and a second therapeutic agent. Accordingly, one of ordinary skill in the art would have been imbued with at least a *reasonable expectation* that gemcitabine and DMXAA in combination would be effective in treating solid tumors.

Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to

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combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering DMXAA in combination with gemcitabine as motivated by Siemann *et al.* and Pruijn *et al.* in view of Grindley *et al.* and van Moorsel *et al.*, one would achieve a method of treating cancer. While *In re Kerkoven* is limited to the mechanical arts, the holdings in this case are pertinent to the present claims because the idea of combining two known anticancer drugs to treat cancer flows logically from the individual drugs being taught to be useful in treating cancer. As such, one skilled in the art would reasonably expect the combination of drugs to also be effective in treating cancer. This is especially true in the present case where the prior art teaches that combinations of DMXAA or gemcitabine with other anticancer agents having different mechanisms of action are effective to treat cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the present case, it is expressly recognized in the prior art that combining DMXAA or gemcitabine with other known anticancer agents would be expected to result in a composition useful for treating cancer.

Finally, it is clear from the prior art that DMXAA potentiates the antitumor effect of a number of anticancer agents (*e.g.* cisplatin, cyclophosphamide and melphalan) because of its mechanism of action (inhibiting tumor blood flow). As such, one skilled in the art would have been imbued with at least a reasonable expectation that DMXAA combined with gemcitabine would be effective as an antitumor composition.

Applicant's arguments have been carefully considered but they are not persuasive.

Firstly, Applicants summarize the teachings of the cited prior art as set forth in the previous Office Action at page 9, ¶4 to page 10 ¶1. The Examiner agrees with Applicant's summary of the prior art teachings.

Secondly, Applicants argue that Siemann do not teach gemcitabine and thus do not teach gemcitabine in combination with DMXAA. The Examiner has already acknowledged that Siemann does not teach combining DMXAA with gemcitabine. However, gemcitabine is taught in Grindley et al. and Van Moorsel et al.

Thirdly, Applicants argue that Pruijn et al. do not teach gemcitabine and do not teach gemcitabine in combination with DMXAA. As with Siemann, the Examiner has already acknowledged that Pruijn does not teach combining DMXAA with gemcitabine. However, gemcitabine is taught in Grindley et al. and Van Moorsel et al.

Fourthly, Applicants argue that Grindley et al. do not teach gemcitabine in combination with another anti-cancer agent, particularly gemcitabine in combination with DMXAA. The Examiner has already acknowledged this fact, explicitly stating in the previous Office Action and reiterated above, “Grindley et al. do not teach combining gemcitabine with other anticancer agents”.

Fifthly, Applicants argue that Van Moorsel et al. do not teach combining gemcitabine with DMXAA. While this is certainly true, Van Moorsel et al. is simply provided as evidence that it was known in the art that gemcitabine could be combined with other anticancer agents for the treatment of cancer. If Van Moorsel et al. taught combining gemcitabine with DMXAA, the reference would have been used in support of a 35 U.S.C. 102 rejection, not a 35 U.S.C. 103 rejection as herein.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the fact that none of the cited references explicitly teaches combining gemcitabine with DMXAA is not pertinent to the present 35 U.S.C. 103 rejection. The cited prior art, in combination, teaches that DMXAA and gemcitabine were both known in the art to be effective anticancer agents and were also both known to be used in combination with other anticancer agents. As such, it would have been *prima facie* obvious to one of ordinary skill in the art that gemcitabine and DMXAA could also be combined with one another for the treatment of cancer.

Applicants argue that neither Siemann nor Pruijn motivate one skilled in the art to pick gemcitabine from all the anti-cancer agents known in the art and use it in combination with DMXAA. In this regard, Applicants argue that mere recitation of cisplatin or cyclophosphamide in combination therapy with DMXAA, as in Siemann, is not a suggestion or motivation to pick gemcitabine in the combination therapy. However, as discussed in the above rejection, the motivation to pick gemcitabine comes not from Siemann or Pruijn, but from Grindley et al. and Van Moorsel et al., who teach that gemcitabine is a known anti-cancer agent that has been combined with other anti-cancer agents for the treatment of cancer.

Applicants argue that Example 1 of the instant application demonstrates that each anti-cancer agent may possess a different synergistic activity with DMXAA. As such, Applicants argue that a person of ordinary skill in the art will have no reasonable expectation of success to choose gemcitabine from a plethora of anti-cancer agents known in the art and use it in combination with DMXAA. However, it is a well-established principle in cancer chemotherapy that anti-cancer agents can be combined with one another in order to improve the therapeutic response. Such combining of known anti-cancer agents is more than routine in the art of chemotherapy and thus the skilled artisan would reasonably expect that if two agents are effective to treat cancer when administered as single agents, then they would also be effective to treat cancer when administered together. Siemann, Pruijn *et al.*, and Van Moorsel *et al.* all teach such combination therapy.

Applicants argue that Grindley et al. do not suggest or motivate a person of ordinary skill in the art to use gemcitabine in combination with other anti-cancer agents let alone DMXAA. As discussed supra, such motivation comes from Van Moorsel et al.

Applicants argue that synergistic combination of two anti-cancer drugs, such as, DMXAA and gemcitabine, is not a predictable field. However, the cited prior art do not support this assertion. Siemann and Pruijn, teach that DMXAA enhances the efficacy of three different anti-cancer agents having different mechanisms of action (cisplatin, cyclophosphamide, and melphalan). Van Moorsel teaches that gemcitabine in combination with etoposide is synergistic. Further, Siemann expressly suggests that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the alkylating agent caused by falling tumor blood flow (page 545, right column,

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last full paragraph). One skilled in the art would have been imbued with at least a reasonable expectation that DMXAA would have this effect on any known anticancer agent, including the instantly claimed gemcitabine.

Applicants argue that the Office has resorted to impermissible hindsight by citing "different arts" to put together the elements of the claimed invention where none of the cited art individually or in combination teach, suggest, or motivate a person of ordinary skill in the art with any reasonable expectation of success to arrive at the claimed invention. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this regard, all of the cited references relate to cancer chemotherapy with DMXAA and gemcitabine, both as single agents and in combination with other anti-cancer agents.

Applicants argue that the rationale for the Examiner's citation of *In re Kerkoven* is baseless because the predictability in the field of mixing detergents (as in *Kerkoven*) is much higher than the predictability of using different drugs in the field of cancer treatment. However, while the fact pattern in *In re Kerkoven* is different than that in the instant application, the rationale behind the court's findings applies in the instant case. One skilled in the art of chemotherapy would expect that two agents which are known to be effective to treat cancer as individual agents would also be effective when administered in combination. Applicants have presented no evidence to rebut this natural presumption, whereas the art cited by the Examiner supports this presumption of effectiveness.

As with their argument against *In re Kerkoven*, Applicants argue that the field of invention in *In re Sernaker* (embroidered emblem) is much more predictable than the predictability of using different drugs in the field of cancer treatment. Applicants further argue that none of the references cited by the Office suggest (expressly or by implication) the combination of gemcitabine with DMXAA. However, as discussed supra, the very fact that the cited prior art teaches that DMXAA enhances the efficacy of three different anticancer agents

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along with the fact the gemcitabine in combination with another anticancer agent results in a synergistic effect would imply that DMXAA and gemcitabine, two known anticancer agents, would also be effective when combined.

Applicants argue that the instant application shows surprising results that DMXAA in combination with gemcitabine demonstrates anti-tumor activity much higher than the anti-tumor activity if each of gemcitabine or DMXAA alone (citing page 32, Example 2). Example 32 of Applicant's disclosure relates to an *in vivo* model wherein human tumor xenografts (PSN1) were established in female nude mice. PSN1 is a pancreatic carcinoma. The mice were treated with 20 mg/kg DMXAA alone, 240 mg/kg gemcitabine alone, or 240 mg/kg gemcitabine + 20 mg/kg DMXAA and PSN1 tumor volume doubling and tripling times (days) were measured. The results demonstrate that the combination of DMXAA and gemcitabine is not "synergistic" but rather is additive. For example, the tumor volume tripling time for DMXAA alone was 6.0 days and for gemcitabine alone was 13.9 days. When given in combination, the tumor volume tripling time was ">17" days. The Examiner is not persuaded that the tumor volume tripling time for the combined therapy is unexpected, especially in view of the fact that Pujn teaches that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the agent caused by falling tumor blood flow. Even if the Examiner were to accept that Applicant's results are unexpected, such results are not commensurate in scope with the claims. The results are limited to a single tumor type (pancreatic carcinoma) whereas the claims broadly recite the treatment of "a solid cancerous tumor".

Accordingly, the claims are deemed properly rejected over the cited prior art as set forth in the previous Office Action and as reiterated above.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Peters et al. (*Pharmacology & Therapeutics*, 2000, vol. 87, pages 227-253) discusses the basis for effective combination cancer chemotherapy with antimetabolites, including gemcitabine. The reference discloses that a new type of combination is that of an antimetabolite

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with inhibitors of angiogenesis. The reference further discloses that gemcitabine has been effectively combined with numerous anticancer agents, including 5-fluorouracil, CDDP, carboplatin, docetaxel, ifosfamide, navelbine, paclitaxel, vinorelbine, etoposide, and doxorubicin.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614